DRAFT

TOBACCO SMOKE CONSTITUENTS

2025822258

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Table of Contents

2025822259

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

I. INTRODUCTION

Tobacco smoke is a highly complex mixture containing, by some estimates, over 4,000 constituents. Over the years, much time and effort has been devoted to determining the identity of tobacco smoke constituents. This has proven difficult, however, and much remains to be learned about the structure and makeup of tobacco smoke and its relationship, if any, to human disease.

Ninety percent of cigarette smoke is air, water and carbon dioxide, a natural by-product of combustion. Of the remaining 10 percent, only a few substances such as nicotine and carbon monoxide (CO) have been measured by researchers as being present in smoke at levels above one milligram per cigarette. Anti-smoking advocates frequently assert that nicotine and CO cause disease in humans. The same is also said about "tar," even though it is a laboratory product, not an actual constituent of tobacco smoke.

The vast majority of the remaining constituents actually present in cigarette smoke, some of which have been identified in "tar," are present only in extremely small amounts, measured in micrograms (millionths of a gram) or nanograms (billionths of a gram) per cigarette. Nonetheless, anti-smoking advocates occasionally single out for public criticism certain smoke constituents other than "tar," nicotine and CO that have, under conditions and at levels vastly different from those to which a human smoker is exposed, been associated with disease in animals or humans. These substances, however, are ubiquitous. Smokers and non-smokers alike

2025822260

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

are exposed to most of these substances every day simply by breathing air, drinking water and eating food.

The significance of smoke constituents to human health, if any, is not yet understood. According to one researcher in the area, "no ingredient [constituent] or group of ingredients [constituents] as found in tobacco smoke have been established as disease producing in smokers."[1]

II. SMOKE CONSTITUENTS

A. "Tar"

"Tar" is not actually in tobacco smoke, although the many inaccurate references to "tar" in smoke may have created that impression. "Tar" is actually a laboratory product obtained by collecting the particulate matter in tobacco smoke, either by passing cigarette smoke through a cold trap at extremely low temperatures or by using filters and a drying process. That may be why this product is sometimes referred to as condensate. However, material collected in this way does not duplicate what humans are exposed to when they smoke. As a report on a meeting of experts in the area noted:

> [T]here is, at present, no available instrumentation permitting the separation and individual collection of the particulate and gas phases which duplicates the precise physico-chemical conditions prevailing in cigarette smoke as it is inhaled.[2]

Despite its apparent lack of relevance to smoking, laboratory-produced "tar" has been used in animal experiments designed to investigate the possible relationship between tobacco smoke and

2025822261

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

cancer. In those experiments, "tar" was repeatedly painted on the shaved backs or ears of test animals over prolonged periods of time. These so-called skin-painting experiments have prompted a great deal of interest, as the tumors which resulted have been said to be evidence that tumors might develop in human lungs from inhaling cigarette smoke.

The results of such animal experiments cannot and should not be extrapolated to the human situation. Even if the "tar" collected by the methods described above were present in cigarette smoke, the "tar" used in skin painting experiments is very different by the time it is studied in the laboratory. That is because after "tar" is collected, it continues to undergo chemical changes as long as it is stored.[3] Furthermore, as an experimental toxicologist has noted, even if an effect such as tumor production is observed in a particular species, that does not necessarily mean that it might "occur either quantitatively or qualitatively in man."[4]

Skin painting experiments suffer from a number of additional weaknesses. For example, the concentrations of "tar" used in such experiments are extremely high. It has been estimated that the amounts utilized would be equivalent to an individual smoking over 100,000 cigarettes per day.[5] Furthermore, the skin and ears of laboratory animals are not similar to human lung tissue. Animal skin lacks the intricate clearance mechanisms of the lungs, such as the mucus blanket which coats the lining of the major air-

2025822262

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

ways of the lung. Even the summary report of a study sponsored by the United States government utilizing skin painting techniques conceded "the uncertain relationship between tumors resulting from mouse skin painted with condensate and human lung cancer."[6] Consequently, such experiments have been characterized as involving applying "the wrong material in the wrong form, in the wrong dosage, to the wrong tissue of the wrong animal."[7]

It is misleading, therefore, to draw definitive conclusions about "tar" and human disease from skin painting studies. As a knowledgeable observer of research in this area has stated: "Bronchogenic carcinoma [lung cancer] has never been produced by tobacco or its products in any experimental animal despite the multiplicity of attempts."[8] (Emphasis added) All in all, the following statement made in the mid-1970's still provides a concise summary of the current state of scientific data concerning "tar":

> Human beings do not smoke 'tar' and laboratory reports on 'tar' yields have not been established as significant to human health.[9]

B. Nicotine

Nicotine is a natural element of tobacco and, thus, is present in tobacco smoke. Nicotine has been described by some researchers as having no known chronic or cumulative effects on human health.[10] The data on the nature of nicotine's relationship to human health is inconclusive at best, because, among other things, science cannot determine with any precision how much nico-

2025822263

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

tine a smoker is exposed to. In fact, no correlation between the nicotine level of a cigarette or the number of cigarettes smoked and the smoker's actual nicotine intake has been conclusively established because of individual variations in puff rates, depth of inhalation, and body metabolism.[11]

Nonetheless, anti-smoking advocates blame nicotine for the development of heart disease. Yet no biological mechanism by which nicotine, or any other agent, may be involved in heart disease has been demonstrated. Serious questions about what role, if any, nicotine plays have been raised as a result of autopsy findings of fatty deposits and other changes in the arteries of individuals who either have not smoked or could have smoked only briefly, such as infants, children, and young men killed in military battle.[12] Even the 1983 U.S. Surgeon General's Report, which focused on cardiovascular disease, concedes that "the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive. . . ."[13] That opinion was shared by a German researcher who has conducted research on the relationship between nicotine and the clogging of arteries. After reviewing the literature, he and his co-author concluded that "there is no established evidence which supports the hypothesis that nicotine has any influence on the development" of those changes.[14] (Emphasis added)

Claims by anti-smoking advocates regarding the role of nicotine in the development of heart disease are further undermined

2025822264

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

by two epidemiological (population) studies. In a study that dealt with myocardial infarction (heart attack), the authors reported finding -- contrary to what they expected -- that the nicotine and carbon monoxide levels of the cigarettes their subjects smoked were not related to the risk of heart attack.[15]

The second study, chaired by a well-known British scientist opposed to cigarette smoking, examined the serum (blood) levels of cotinine, a nicotine metabolite, in male nonsmokers and smokers of cigarettes only, cigars only, and pipes only. The study determined that the mean cotinine level for pipe smokers was significantly higher than the levels for cigarette and cigar smokers. Since studies of pipe smokers generally have not reported an increased risk of coronary heart disease, the researchers concluded that "nicotine is unlikely to be the major cause of the excess coronary heart disease mortality in cigarette smokers."[16] After re-evaluating their methodology in response to anti-smoking criticism of their study, the researchers again concluded that they were "reasonably confident" that "exposure to high systemic concentrations of nicotine is not a cause of the disease." Although the researchers quibbled with the result of their own study, arguing that their data "cannot completely exonerate" nicotine, they added that the data do "substantially reduce the weight of evidence suggesting that nicotine is a cause of coronary heart disease."[17]

Animal studies which purport to establish a causal role for nicotine in heart disease have been soundly criticized for their

2025822265

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

unrealistic and excessive test conditions. An American researcher who conducted animal studies on this subject has noted:

> There have been some studies that have exhibited minor or questionable changes with the use of an equivalent dose of 600 or more cigarettes a day in man. This is such a large number that I think man would find it difficult to find the time to smoke them.[18]

In contrast, this researcher concluded that animal studies using realistic doses of nicotine have "failed to initiate, exacerbate, or otherwise influence" the process leading to the clogging of arteries in test animals.[19] In one such study, which was funded by the United States government, male beagle dogs fed a special diet to induce this process were exposed for two years to cigarette smoke containing low or high levels of nicotine and, in some cases, enriched with carbon monoxide. According to the final report of the research laboratory which conducted the study, "the results of this study lent no support to the suggestion that cigarette smoking increases the rate of development" of this process.[20]

The foregoing demonstrates the validity of one researcher's summary: "While many studies have been done in this field, none have established nicotine as contributing to the causation, aggravation or precipitation of any cardiovascular disease."[21] (Emphasis added)

2025822266

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

C. Carbon Monoxide

Carbon monoxide (CO) is a tasteless, odorless, colorless gas produced by many natural and man-made sources, including automobile exhaust and industrial emissions. It is naturally produced by the body during daily metabolism. Burning cigarettes also produce CO, but that amount has been described as "insignificant" compared to most other sources.[22] Nonetheless, CO has received considerable attention in the scientific literature, usually in regard to cardiovascular disease (CVD). In a review of such literature, however, two public health specialists concluded that "despite the large amount of literature available, the conclusions that can be drawn as to the role of CO in human CVD remain tentative and open to varying interpretations."[23] This conclusion is supported by a similar statement in the 1983 U.S. Surgeon General's Report, which focused on heart disease:

> Carbon monoxide is another major component of cigarette smoke for which there are some data supporting a possible atherogenic [plaque forming inside the arteries] role; however, a review of recent literature on the role of carbon monoxide in arterial injury and atherogenesis leads to no consensus.[24]

The conclusion of another group which also reviewed the literature was more concise. The chairman of the American Heart Association Task Force on Environment and the Cardiovascular System reported that his group had concluded that the question of whether CO causes heart disease "remains unanswered even at the basic science level."[25] (Emphasis added)

2025822267

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Specialists who reviewed these and other studies have concluded that "there is no evidence" to support the suggestion that exposure to low or moderate levels of CO increases the rate of development of atherosclerotic disease in man. Indeed, they contend that "sufficient evidence is available to support the conclusion that, in fact, CO is not of pathogenetic [disease causing] consequence in atherosclerotic disease."[26] (Emphasis added)

D. Other Constituents*

Over the years, the principal focus of the attention and concern of smoking critics has been on "tar," nicotine and CO. One researcher who has tried to establish a causal link between smoking and disease, however, concluded with reference to these substances that:

> We assume that it is the tar which causes lung cancer, but we do not know this for certain.
>
> Until now, we have implicated nicotine in the development of cardiovascular diseases, but we cannot prove this.
>
> The same is true for CO.[27]

Thus, some anti-smoking advocates have attempted to shift public attention to the presence of other substances in cigarette smoke. These substances, as found in cigarette smoke (like "tar," nicotine, and CO), have not been scientifically proven to cause any disease in humans. Nonetheless, these constituents are of interest

---

* A more detailed discussion of specific constituents appears in Appendix A to this paper.

2025822268

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

because at levels and under conditions of exposure greatly different than those encountered by the smoker, certain of these compounds may have a toxic effect on or may be associated with disease in animals or humans.

It is an axiom among toxicologists that any substance is toxic if the level of exposure is high enough and no substance is toxic if the level of exposure is low enough.[28] The amount of substances other than nicotine and CO in cigarette smoke is extremely low, measured in terms of micrograms and nanograms per cigarette. As previously noted, a microgram is one-millionth of a gram, the equivalent of one second in twelve days. A nanogram is one billionth of a gram, the equivalent of one second in thirty-two years.

Moreover, these substances are for the most part natural by-products of combustion of any organic matter, including tobacco, or are found in any organic matter whether or not that matter is burned. Likewise, other compounds present in smoke are also present in the air we breathe and the water we drink. Thus, it is scientifically inaccurate to state as "fact" that there is something "unique" about the presence of these substances in cigarette smoke.

2025822269

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

III. CONCLUSION

Numerous claims have been made about the relationship between cigarette smoke constituents and the health of the smoker. However, such claims are just that -- claims which are not supported by reliable scientific proof. After years of study, no scientific relationship has been established between "tar," nicotine and carbon monoxide and human disease. Other constitutents, detectable at extremely low levels in cigarette smoke, are the subject of occasional public comment. These substances are not unique to tobacco smoke, however, and as with "tar," nicotine and CO, have not been proven to cause disease in humans in the form in which they are found in cigarette smoke.

2025822270

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

REFERENCES

1. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 152-167 (at 155), February 19, March 24, and May 27, 1976.

2. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, "Chapter 12. Harmful Constituents of Cigarette Smoke," The Health Consequences of Smoking: A Reference Edition, HEW Publication No. (CDC) 78-8357, Washington, D.C., U.S. Government Printing Office, 621-634 (at 625), 1976.

3. Schönherr, H., Klimisch, H.-J., and Harke, H.-P., "Alterung von Cigarettenrauchkondensat: Quantitative Untersuchungen der Artefaktbildung durch Gas- und Partikelphasenreaktionen (Aging of Cigarette Smoke Condensate: Quantitative Investigation of Artifact Formation Via Gas and Particle Phase Reactions)," Bieträge zur Tabakforschung 7(1): 18-23, January, 1973. Translation.

   Dube, M.F. and C.R. Green, "Methods of Collection of Smoke for Analytical Purposes." In: Recent Advances in Tobacco Science, Published Proceedings of The 36th Tobacco Chemists' Research Conference, Volume 8, 42-102, October 25, 1982.

4. Hine, C.H., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 127-145 (at 138), February 19, March 24 and May 27, 1976.

5. Macdonald, I.G., Statement, Re: "False and Misleading Advertising (Filter-Tip Cigarettes)." In: Hearings Before the Committee on Government Operations, Subcommittee on Legal and Monetary Affairs, United States House of Representatives, Eighty-Fifth Congress, First Session, 224-240, July 18, 19, 23, 24, 25 and 26, 1957.

   Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-Second Congress, Second Session, 97-122 (at 102), February 1, 3, and 10, 1972.

2025822221

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

6. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute Smoking and Health Program, Report No. 5: Toward Less Hazardous Cigarettes. Summary: Four Skin Painting Bioassays Using Condensate From Experimental Cigarettes, 1-29 (at 2), September, 1980.

7. Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-Second Congress, Second Session, 97-122 (at 102), February 1, 3, and 10, 1972.

Hockett, R.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Seventh Congress, Second Session, 627-635 (at 635), March 5, 11 and 12, 1982.

8. Hockett, R.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 841-851 (at 844), March 9 and 17, 1983.

9. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 152-167 (at 154), February 19, March 24, and May 27, 1976.

10. Hockett, R.C., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 146-151, February 19, March 24, and May 27, 1976.

Hine, C.H., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 127-145, February 19, March 24 and May 27, 1976.

11. Langone, J.J., Gjika, H.B. and Van Vunakis, H., "Nicotine and Its Metabolites. Radioimmunoassays for Nicotine and Cotinine," Biochemistry 12(24): 5025-5030, 1973.

2025822272

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

12. Benditt, E.P., "The Origin of Atherosclerosis," Scientific American 236(2): 74-85, February, 1977.

Blumenthal, S., Jesse, M.J., Hennekens, C.H., Klein, B.E., Ferrer, P.L. and Gourley, J.E., "Risk Factors for Coronary Artery Disease in Children of Affected Families," The Journal of Pediatrics 87(6, Pt. 2): 1187-1192, December, 1975.

Newman, W.P., Freedman, D.S., Voors, A.W., Gard, P.D., Srinivasan, S.R., Cresanta, J.L., Williamson, G.D., Webber, L.S. and Berenson, G.S., "Relation of Serum Lipoprotein Levels and Systolic Blood Pressure to Early Atherosclerosis: The Bogalusa Heart Study," New England Journal of Medicine 314(3): 138-144, January 16, 1986.

Rifkind, B.M. and Lenfant, C., "Cholesterol Lowering and the Reduction of Coronary Heart Disease Risk," Journal of the American Medical Association 256(20): 2872-2873, November 28, 1986.

Strong, J.P., "Coronary Atherosclerosis in Soldiers: A Clue to the Natural History of Atherosclerosis in the Young," Journal of the American Medical Association 256(20): 2863-2866, November 28, 1986.

Enos, W.F., Holmes, R.H. and Beyer, J., "Coronary Disease Among United States Soldiers Killed in Action in Korea: Preliminary Report," Journal of the American Medical Association 152(12): 1090-1093, July 18, 1953.

Enos, W.F., Beyer, J.C. and Holmes, R.H., "Pathogenesis of Coronary Disease in American Soldiers Killed in Korea," Journal of the American Medical Association 158(11): 912-914, July 16, 1955.

Enos, W.F., Holmes, R.H. and Beyer, J.C., "Pathology of Coronary Arteriosclerosis," The American Journal of Cardiology 9(3): 343-354, March, 1962.

McNamara, J.J., Molot, M.A., Stremple, J.F. and Cutting, R.T., "Coronary Artery Disease in Combat Casualties in Vietnam," Journal of the American Medical Association 216(7): 1185-1187, May 17, 1971.

13. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 2. Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, DHHS Publication No. (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, 13-62 (at 50), 1983.

2025822273

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

14. Schievelbein, H. and Heinemann, G., "Nicotine and Atherosclerosis." In: Atherosclerosis VI: Proceedings of the Sixth International Symposium, F.G. Schettler, A.M. Gotto, G. Middelhoff, A.J.R. Hablnicht and K.R. Jurutka (eds.). Berlin, Springer-Verlag, 899-902 (at 901), 1983.

15. Kaufman, D.W., Helmrich, S.P., Rosenberg, L., Miettinen, O.S. and Shapiro, S., "Nicotine and Carbon Monoxide Content of Cigarette Smoke and the Risk of Myocardial Infarction in Young Men," The New England Journal of Medicine 308(8): 409-413, February 24, 1983.

16. Wald, N.J., Idle, M. and Boreham, J., "Serum Cotinine Levels in Pipe Smokers: Evidence Against Nicotine as Cause of Coronary Heart Disease," The Lancet II(8250): 775-777 (at 775), October 10, 1981.

17. Wald, N.J., Idle, M., Boreham, J., Bailey, A and Van Vunakis, H., "Urinary Nicotine Concentrations in Cigarette and Pipe Smokers," Thorax 39(5): 365-368 (at 368), 1984.

18. Fisher, E.R., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 406-423 (at 407), March 9 and 17, 1983.

19. Fisher, E.R., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 406-423 (at 407), March 9 and 17, 1983.

20. Hazleton Laboratories America, Inc., "Final Report. Inhalation Bioassay of Cigarette Smoke in Dogs: Effects of Nicotine and Carbon Monoxide on Atherogenesis," Project No. 976-904, Contract No. ECI-SHP-75-112, Submitted to the National Cancer Institute, Division of Cancer Cause and Prevention, Smoking and Health Program, Washington, D.C., 1-31 (at 5-6), June 10, 1981.

21. Hockett, R.C., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 146-151 (at 147), February 19, March 24, and May 27, 1976.

2025822274

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

22. Wakeham, H.R.R., "Environmental Carbon Monoxide from Cigarette Smoking -- A Critique," Preventive Medicine 6: 526-534 (at 526), 1977.

23. Weir, F.W. and Fabiano, V.L., "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes," Journal of Occupational Medicine 24(7): 519-525 (at 520), July, 1982.

24. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 2. Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, DHHS Publication No. (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, 13-62 (see particularly 51), 1983.

25. Gonzalez, E.R., "No Proof of Environmental Ill Effects on Heart," Journal of the American Medical Association 243(12): 1219-1220 (at 1219), March 28, 1980.

26. Weir, F.W. and Fabiano, V.L., "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes," Journal of Occupational Medicine 24(7): 519-525 (at 523), July, 1982.

27. Astrup, P., Quoted in "Zigaretten, Nikotin und Kohlenmonoxid. Wie kann man Raucherschäden mindern? (Cigarettes, Nicotine and Carbon Monoxide. How Can Harm to Smokers Be Reduced?)," UMSCHAU 79(1): 11-18, 1979. Translation, p. 21.

28. Doull, J. and Bruce, M.C., "Chapter 1. Origin and Scope of Toxicology." In: Casarett & Doull's Toxicology. The Basic Science of Poisons. Third Edition. New York, Macmillan Publishing Company, 3-10 (see particularly 3), 1986.

2025822275

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

APPENDIX A

OTHER CONSTITUENTS

2025822276

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

I. INTRODUCTION

The following is a brief discussion of other constituents in cigarette smoke sometimes referenced by anti-smokers. As stated previously, the vast majority of such constituents, some of which have been identified in "tar," are present in cigarette smoke only in extremely small amounts. As is the case with "tar," nicotine and CO, these minute subfractions of tobacco smoke have not been scientifically proven to cause human disease as they are encountered by the smoker.

II. OTHER CONSTITUENTS

Acetaldehyde

Acetaldehyde is reportedly present in cigarette smoke in minute quantities. It is a chemical compound related to ethanol and is used in the manufacturer of plastics and synthetic rubber. Acetaldehyde is also commonly found in perfume.[1] Exposure to extremely high levels of acetaldehyde has an eye and skin irritant effect, and may be toxic.[2] However, an international research group recently concluded that the data was "inadequate" to support any claim that acetaldehyde causes cancer in humans at any level of exposure.[3]

Acetone

Acetone has been reported to be present in minute quantities in the "vapor phase" of cigarette smoke, i.e., it is not found in "tar" (smoke condensate). It is most commonly encountered

2025822277

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

either at work or at home in the form of cleaning solvent. It has also been detected in freeze-dried foods and dried milk. Moreover, acetone is a naturally occurring constituent of human blood and urine.[4]

Acetone is not considered toxic at low levels of exposure, although at higher levels of exposure it can be an eye or skin irritant.[5] One researcher reported that he was unable to produce tumors through the mouse-skin painting method using acetone.[6]

Acrolein

Acrolein has been reported to be present in small quantities in the vapor phase of cigarette smoke. It is also everywhere in the environment as a product of fires, automobile exhaust, and other industrial emissions. Acrolein is also produced by burning foods containing fat, such as grilling a steak.[7] Although at high concentrations acrolein may have a toxic or irritant effect, one recent review of the research conducted regarding acrolein's toxicity or carcinogenicity in humans concluded "there is no evidence to support that acrolein is a human carcinogen."[8]

Ammonia

Ammonia is reportedly detectable in minute amounts in cigarette smoke. It occurs naturally as a part of protein metabolism in man and in virtually all species of animals. Ammonia is widely used as a fertilizer. It is also a common household clean-

2025822278

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

ser.[9] At high concentrations, ammonia can have a strong irritant effect and cause burns; its pungent odor, of course, is very familiar. One researcher, however, recently noted that:

> The biologic significance of inhaled ammonia in the concentrations generated in mainstream smoke, which are very low, is purely conjectural.[10]

Arsenic

Arsenic is a naturally occurring metal that is drawn into growing tobacco (and other plants) from the soil. It is present also in rocks, water, and virtually all living organisms in concentrations of parts per million and parts per billion. The United States government has estimated that non-smokers generally take in up to 60 micrograms of arsenic per day from various sources; it has also estimated that smokers take in an additional two micrograms of arsenic per pack of cigarettes smoked, thus increasing their daily arsenic intake only marginally.[11] One recent literature review noted that over 99% of the arsenic (and other metals such as lead and cadmium) in tobacco remains in cigarette ash.[12]

Analyses of the literature regarding the relationship between exposure to arsenic and disease have generally been inconclusive. For example, in a recent review of the literature, a researcher characterized "its claimed effects on human smokers as speculative."[13] The 1982 U.S. Surgeon General's Report also noted that "the view that inorganic arsenicals cause cancer of the skin and lung has not been widely accepted. . . ."[14]

2025822279

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Benzene

Benzene has been reported to be present in the vapor phase of cigarette smoke in small quantities. Although benzene has sometimes been suggested as a possible cause of leukemia, leukemia has not been consistently related to cigarette smoking in the various statistical studies that form the primary basis for public health criticism of smoking.[15] The U.S. Surgeon General has also noted that "no dose-response relationship has been established between death rate from leukemia and number of cigarettes smoked."[16]

Benzo(a)pyrene

Benzo(a)pyrene (BaP) is sometimes singled out as a possible human carcinogen because it is a component of the laboratory product "tar;" "tar," as noted above, can produce tumors under the highly artificial conditions involved in animal skin painting experiments. Claims that BaP, and other polycyclic aromatic hydrocarbons (such as dibenzacridine), can cause cancer in humans thus suffer from the same weaknesses as those claims generally directed at "tar."

BaP is formed by the incomplete combustion of organic matter. In addition to cigarette smoke, other sources of BaP in the atmosphere are coal and oil fired power stations, domestic heating, industrial processes and emissions, automobile emissions, and forest fires and volcanic activity. Atmospheric BaP is carried into the soil, the water table, and the ocean through rainfall.

2025822280

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Thus, BaP is detectable in fish, meat and vegetables, as well as in drinking water. Foodstuffs as varied as coconut oil, sardines, and cheese all contain BaP at relatively high levels. Charcoal-grilled meats have been reported to contain particularly high levels of BaP.[17] Two researchers concluded that the BaP concentration in a single charcoal-grilled steak was equivalent to that in the smoke of 600 cigarettes.[18] The daily levels of exposure to BaP simply from breathing the air in some cities has been estimated, by a former U.S. Surgeon General, to be approximately twice as high as that for a cigarette smoker.[19]

Butane

Butane may be present in the vapor phase of cigarette smoke in minute quantities. It occurs in natural gas and is present in the atmosphere as the result of the combustion of gasoline and other petroleum products. Butane is also frequently used as an aerosol propellant. The inhalation of butane has not been demonstrated to produce disease in humans.[20]

Cadmium

Cadmium is a trace "heavy metal" that has been reported to be present in tobacco and in cigarette smoke in certain compound forms. It is used extensively in the production of cadmium-copper alloys and corrosion-resistant coatings. It is found in alkaline batteries, glass, solder, paint pigments and some pesticides and

2025822281

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

fungicides. The principal sources of cadmium exposure for man are in food, dairy products and drinking water.[21]

It has been estimated that in most countries the average smoker is exposed to approximately the same amount of cadmium daily through smoking as he or she is through diet.[22] Other researchers recently concluded that the amount of cadmium in two packs of cigarettes, even if entirely inhaled, would still be less than would be inspired in two hours of breathing atmospheric cadmium at the maximum safe levels established by the health authorities of several countries.[23]

Cadmium has been identified as a possible tumor promotor under experimental conditions in animals. Three German researchers recently observed, however, that the results of these experiments should not be extrapolated to humans because the doses necessary to induce tumor production corresponded to smoking between 5,000 to 20,000 cigarettes per day.[24] Similarly, a recent review of the literature concerning the claimed carcinogenicity of cadmium noted that "evidence for potential cadmium carcinogenicity in humans in the dosages delivered from smoking is very limited."[25]

Chromium

Chromium is a metal that is reportedly detectable in trace amounts in tobacco. Like the other trace metals in tobacco, it is drawn into the growing plant from the soil. Also like the other metals in tobacco, it is estimated by one researcher that

2025822282

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

over 99% of the chromium in tobacco remains in cigarette ash and is not transferred into smoke.[26] A group of researchers recently concluded that "[t]here is no indication . . . that the chromium [in tobacco] goes to the mainstream smoke."[27] (Emphasis added)

Chromium is a naturally occurring element of rock; as rock is weathered into soil, the chromium is transferred into the soil as well. From the soil, chromium is both washed into the oceans, where it is incorporated into the oceanic food-chain, and it is taken up by growing plants and incorporated into the land food-chain. Chromium compounds are also present in the atmosphere as a result of industrial emissions of the burning of organic matter.[28] Food is the principal environmental source of chromium intake by man, with vegetables, unrefined sugar, beef, liver, eggs and animal fats generally having the highest concentrations.[29]

Studies of various illnesses developed by workers in the chromate industry, who were exposed to large concentrations of chromium compounds over many years, have raised concerns about chromium as a possible cause of chronic disease in humans.[30] These studies have been subject to scientific criticism.[31] Given the extremely low level, if any, to which a smoker is exposed to chromium beyond his or her normal dietary and environmental chromium intake, according to one researcher "its role as a potential carcinogen in human smokers is not known."[32]

2025822283

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Hydrogen Cyanide

Hydrogen cyanide (HCN) is also reportedly present in minute amounts in the vapor phase of cigarette smoke. It is produced by the combustion of the amino acids in tobacco. HCN is also generated by the combustion of carbon materials in air, for example, during home cooking. HCN is used in a variety of industrial processes and is also present in such varied food products as bitter almonds, lima beans, soybeans, apricots, and linseed. It has been detected in certain wines.[33]

A recent study noted that although the HCN level detectable in smokers' blood is slightly elevated after smoking, it is rapidly eliminated from the system.[34] Another reviewer concluded that the effect of HCN in cigarette smoke, if any, on humans "remains to be determined."[35]

Lead

Lead, like the other trace metals reportedly present in tobacco, is drawn from the soil into the growing plant. Also like the other trace metals, one researcher estimated that less than one percent of the lead in the tobacco is transferred to the smoke, with the remainder left in the ash.[36] Lead is present in the air, soil and water. Hence, smokers and non-smokers alike are exposed to and ingest small amounts of lead each day. One research group has estimated that a smoker will ingest five nanograms of lead from a pack of cigarettes; the dietary intake of lead per day,

2025822284

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

however, is much higher, ranging between 100-500 nanograms per day.[37]

Numerous health concerns have been expressed regarding exposure to high levels of lead and lead compounds. However, given the very low levels of lead exposure from tobacco, one researcher concluded that "the role of lead as a potential carcinogen for human smokers is not known."[38]

Methanol

Methanol is reported to be present in very small quantities in cigarette smoke as a vapor phase component. It is used in enamels, dyes, stains, cleaning solvents, paint and varnish removers, antifreeze mixtures, and as fuel for internal combustion engines. It is also present in bread, soy sauce and various fruits and vegetables.[39]

Methanol can be a skin and eye irritant in large concentrations. One researcher recently noted, however, that "[c]onsidering the dose of methanol estimated to be toxic to humans (1 g/kg), it is unlikely that a normal human being could ever be exposed to enough of it by inhalation to experience acute toxicity."[40] This scientist also noted that he had been unable to find any studies showing the inhalation of methanol to be carcinogenic.

2025822285

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Naphthalene

Naphthalene is a substance related to benzene. It is reportedly present both in "tar" and in the vapor phase of cigarette smoke in small quantities, and is generated by the combustion of tobacco. Naphthalene is used extensively in the chemical, plastics and dye industries. In the home, it is found frequently in air fresheners, moth balls, varnishes and wood preservatives. Radishes also contain naphthalene.[41] Naphthalene has no conclusive reported carcinogenic effect, although it is sometimes associated with leukemia in animal experiments. As noted above, leukemia has not been consistently statistically associated with cigarette smoking.[42]

Nickel

Nickel, like arsenic, is drawn from the soil into growing tobacco. Also like arsenic, it is estimated that 99% of the nickel in tobacco remains in the ash of a cigarette, and is not transferred to the smoke. The U.S. Surgeon General has concluded that "it is not likely that nickel plays a significant role in the etiology of lung cancer in cigarette smokers. . . ."[43] Other researchers and reviewers have reached the same conclusion.[44]

2025822286

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Nitrogen Oxides

Cigarette smoke reportedly contains nitric oxide (NO), but "very little, if any," nitrous oxide or nitrogen dioxide.[45] The U.S. Surgeon General has noted data showing that both smokers and nonsmokers maintain "a consistently low level" of NO in their blood and has suggested that the "lack of a significant difference" between the two groups indicates that NO from external sources "appears to have little effect" on the amount found in the blood.[46]

Nitrosamines

Nitrosamines reportedly are detectable in both "tar" and in the vapor phase component of cigarette smoke. The presence of nitrosamines in cigarette smoke is often the subject of public comment by anti-smoking advocates because, under experimental conditions, certain nitrosamine compounds can produce tumors in laboratory animals. As two reviewers of the literature noted, however, "direct epidemiologic evidence that would associate nitrosamines with human cancer is very limited."[47] Another recent reviewer suggested that:

> The role of nitrosamines in the pathogenesis of human lung cancers is theoretical, and it is yet to be shown conclusively that any specific N-nitroso compound causes human cancer.[48]

Even the U.S. Surgeon General has stated that there is "a lack of direct evidence" that the nitrosamines specific to tobacco have any proven health effect on smokers.[49]

2025822287

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

The components of nitrosamines -- nitrates, nitrites and amines -- are naturally occurring substances. Hence, nitrosamines are found in soil, air, water and food. Beer and scotch whiskey have recently been determined to contain dimethylnitrosamine.[50] Foods often prepared with nitrites (used as a preservative) include ham, sausages, bacon, luncheon meats and frankfurters; seafood and cheese also often contain nitrosamines.[51]

Phenol

Phenol is reported to be present in minute quantities in cigarette smoke and is detectable in "tar." It has a variety of industrial uses, including the manufacture of perfumes, plastics and fertilizers. Phenol occurs naturally in animal tissues; the consumption of meat has been identified as the primary source of human exposure to phenol. It is also present in drinking water.[52] Two reviewers of the literature concluded that "[t]here is no specific evidence of human cancer attributable to phenol or related compounds. . . ."[53] A group of researchers likewise reported that phenol is not present in cigarette smoke at high enough concentrations to cause disease in smokers.[54]

Polonium-210

Polonium-210 is a radioactive element that has been reported to be present in trace amounts in tobacco and cigarette smoke. It is also present in the atmosphere and in soil -- both

2025822288

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

as a part of the earth's natural background radiation and as a result of nuclear testing -- from which it is presumably drawn into growing tobacco. Smoking critics often cite the presence of polonium-210 in smoke as significant because it, along with most other radioactive materials, can have adverse health effects in humans and in animals if the exposure is of sufficient intensity. Even the U.S. Surgeon General, however, has questioned the significance of polonium-210 to lung cancer in humans.[55] Other researchers have disputed the conclusion drawn by some scientists that polonium-210 accumulates in the lung tissue of smokers.[56] Additional researchers discount the claimed risk to smokers of inhaled polonium, noting the extraordinarily minute quantities at which it is present.[57]

Toluene

Toluene is reported to be a constituent of the vapor phase component of cigarette smoke. It is present in the atmosphere as a result of industrial emissions, automobile emissions, and gasoline evaporation. Exposures at home include inks, dyes, and perfumes.[58] Although it is an eye and skin irritant at low levels and concentrations, toluene has not been reported to be toxic or to cause chronic disease in humans at those levels.[59]

2025822289

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Urethane

Urethane (ethyl carbamate) has been reported to be present in cigarette smoke in very small amounts. It has been widely used in the plastics and textile industries. It is also used in a variety of agricultural chemicals, pesticides, fungicides, and in some therapeutic drugs. Urethane is a natural by-product of fermentation, and is found in wines, distilled spirits, and beer, as well as in fermented food products such as cheese, yogurt and soy sauce.[60] The U.S. Surgeon General has conceded that urethane, although possibly an animal carcinogen, is not present in cigarette smoke in sufficient quantities to cause cancer in smokers.[61]

Vinyl Chloride

Vinyl chloride is reportedly present in minute amounts in the vapor phase of cigarette smoke. Although it is a gas, it is detectable in various food products such as honey, butter and tomato ketchup. It is also present in some wines.[62] Vinyl chloride is also used in the manufacture of plastics.[63]

Vinyl chloride has been reported to have toxic and carcinogenic effects in animals at high concentrations; a similar effect on humans has been suggested. One group of oncologists, however, although subscribing to the general theory that smoking causes cancer, conceded that:

> Based on human data and results from animal studies, it appears to us that the[] minute amounts of [vinyl chloride in cigarette smoke] will not contribute to a measurable degree to

2025822290

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

the carcinogenic activity of tobacco smoke.[64]

This conclusion was echoed by a recent literature reviewer, who concluded that vinyl chloride is present in cigarette smoke "apparently at levels too low to be considered a carcinogen or fibrosis-inducing agent."[65]

2025822291

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

REFERENCES

1. "Hazardous Materials: Acetaldehyde," Dangerous Properties of Industrial Materials Report 9(6): 30-45, 1989.

2. "Hazardous Materials: Acetaldehyde," Dangerous Properties of Industrial Materials Report 9(6): 30-45, 1989.

Brabec, M.J., "Chapter Thirty-Seven. Aldehydes and Acetals." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 2629-2669 (see particularly 2633, 2646), 1982.

3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, "Acetaldehyde (Group 2B)," IARC Monographs On the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenecity: An Updating of IARC Monographs Volumes 1 to 42, Supplement 7, 77-78 (at 77), 1987.

4. Krasavage, W.J., O'Donoghue, J.L., and DiVincenzo, G.D., "Ketones." In: Chapter Fifty-Six. Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 4709-4800 (see particularly 4726), 1982.

Kayaert, G., Tobback, P., Maes, E., Flink, J. and Karel, M., "Retention of Volatile Organic Compounds in a Complex Freeze-Dried Food Gel," Journal of Food Technology 10(1): 11-18, 1975.

Maier, H.G., "Zur Bindung flüchtiger Aromastoffe an Lebensmittel. VI. Mitteilung. Einfache Ketone (Binding of Volatile Aroma Constituents in Foods. VI. Continuation. Simple Ketones)," Zeitschrift Für Lebensmittel -Untersuchung und -Forschung 149(2): 65-69, 1972. English Summary.

5. Krasavage, W.J., O'Donoghue, J.L., and DiVincenzo, G.D., "Ketones." In: Chapter Fifty-Six. Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 4709-4800 (see particularly 4724-4726), 1982.

6. Bock, F.G., Swain, A.P. and Stedman, R.L., "Composition Studies on Tobacco. XLI. Carcinogenesis Assay of Subfractions of the Neutral Fraction of Cigarette Smoke Condensate," Journal of the National Cancer Institute 44(6): 1305-1310, 970.

2025822292

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

7. Beauchamp, R.O., Andjelkovich, D.A., Kligerman, A.D., Morgan, K.T. and Heck, H.d'A., "A Critical Review of the Literature on Acrolein Toxicity," CRC Critical Reviews in Toxicology 14(4): 309-380, 1985.

Sakata, T., Smith, R.A., Garland, E.M. and Cohen, S.M., "Rat Urinary Bladder Epithelial Lesions Induced by Acrolein," Journal of Environmental Pathology, Toxicology, and Oncology 9(2): 159-169, 1989.

Feron, V.J., and Kruysse, A., "Effects of Exposure to Acrolein Vapor in Hamsters Simultaneously Treated with Benzo[a]pyrene or Diethylnitrosamine," Journal of Toxicology and Environmental Health 3(3): 379-394, 1977.

8. Beauchamp, R.O., Andjelkovich, D.A., Kligerman, A.D., Morgan, K.T. and Heck, H.d'A., "A Critical Review of the Literature on Acrolein Toxicity," CRC Critical Reviews in Toxicology 14(4): 309-380 (at 342), 1985.

9. Wands, R.C., "Chapter Forty-One. Alkaline Materials: 1. Ammonia, NH_3, Ammonium Hydroxide, NH_4OH, and Ammonium Salts." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3045-3052, 3067-3069, 1982.

10. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 316), October, 1989.

11. Stokinger, H.E., "Chapter 29. The Metals: 3. Arsenic, As." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 1517-1531, 1982.

Environmental Protective Agency, United States Government, "Health Assessment Document for Inorganic Arsenic," 9-3 to 9-4, 1984.

National Academy of Sciences, Arsenic, 4, 1977.

12. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

13. Huber, G.L, "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars

2025822293

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.

14. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 211), 1982.

15. Huber, G.L., "Physical, Chemical, and Biological Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312, 316), October, 1989.

16. U.S. Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, "Chapter 14. Constituents of Tobacco Smoke: Benzenes and Naphthalenes," Smoking and Health. A Report of the Surgeon General, DHEW Publication No. (PHS) 79-50066, Washington, D.C., U.S. Government Printing Office, 49, 51 (at 51), 1979.

17. Osborne, M.R. and Crosby, N.T., "Occurrence of Benzopyrenes in the Environment." In: Benzopyrenes. M.M. Coombs, J. Ashby, R.F. Newbold and H. Baxter (eds.). Cambridge, Cambridge University Press, Chapter 17, 301-316, 1987.

Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 4. Tri- and Polynuclear Ring Systems." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3253-3431 (see particularly 3345), 1982.

18. Lijinsky, W. and Shubik, P., "Benzo(a)pyrene and Other Polynuclear Hydrocarbons in Charcoal-Broiled Meat," Science 145(2): 53-55, 1964.

19. Burney, L.E., "Governmental Responsibilities in Environmental Health," Public Health Reports 76(4): 291-295 (see particularly 293) April, 1961.

20. Sandmeyer, E.E., "Chapter Forty-Five. Aliphatic Hydrocarbons. 1.5. Butanes." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3182-3183, 1982.

Beall, J.R. and Ulsamer, A.G., "Toxicity of Volatile Organic Compounds Present Indoors," Bulletin of The New York Academy

2025822294

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

of Medicine 57(10): 978-997 (see particularly 980), December, 1981.

21. Stokinger, H.E., "Chapter Twenty-Nine. The Metals: 7. Cadmium, Cd." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 1563-1582, 1982.

Kendrey, G. and Roe, F.J.C., "Cadmium Toxicology," The Lancet, 1206-1207, June 14, 1969.

Gloag, D., "Contamination of Food: Mycotoxins and Metals," British Medical Journal 282(6267): 879-882, March 14, 1981.

22. Lewis, G.P., Jusko, W.J., Coughlin, L.L., and Hartz, S., "Contribution of Cigarette Smoking to Cadmium Accumulation in Man," The Lancet 1(7745): 291-292, February 5, 1972.

Elinder, C.G., Kjellstrom, T., Lind, B., Linnman, L., Piscator, M. and Sundstedt, K., "Cadmium Exposure From Smoking Cigarettes: Variations With Time and Country Where Purchased," Environmental Research 32(1): 220-227, October, 1983.

Scherer, G. and Barkemeyer, H., "Cadmium Concentrations in Tobacco and Tobacco Smoke," Ecotoxicology and Environmental Safety 7(1): 71-78, February, 1983.

Westcott, D.T. and Spincer, D., "The Cadmium, Nickel and Lead Content of Tobacco and Cigarette Smoke," Beiträge zur Tabakforschung 7(4): 217-221, April, 1974.

23. Hennigar, G.R. and Gross, P., "Chapter 5: Drug and Chemical Injury -- Environmental Pathology." In: Anderson's Pathology. J.M. Kissane (ed.). St. Louis, C. V. Mosby Company, Volume 1, 147-238 (see particularly 207), 1985.

24. Schmidt, J.A., Fischbach, E.-D. and Burkart, F., "Cadmium-Untersuchungen im Bereich von Umwelt-, Boden- und Sorteneinflüssen bei Tabak sowie der Cadmium-Übergang in den Zigarettenrauch (A Study of the Influences of Environment, Soil and Varieties on Cadmium Contents in Tobacco and of Cadmium Transfer into Cigarette Smoke)," Zeitschrift für Lebensmittel -Untersuchung und -Forschung 180(4): 306-311, 1985. English Summary and Translation.

25. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.

2025822295

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

26. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

27. Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125 (at 89), 1987.

28. WHO Expert Committee on International Programme on Chemical Safety (IPCS), "3. Sources in the Environment, Environmental Transport and Distribution," Environmental Health Criteria 61: Chromium, Geneva, World Health Organization, 32-41, 1988.

Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125, 1987.

29. Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125, 1987.

30. Stokinger, H.E., "Chapter Twenty-Nine: The Metals. Section 9, Chromium, Cr." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 1589-1605 (see particularly 1601), 1981.

31. Gerhardsson, L., Wester, P.O., Nordberg, G.F. and Brune, D., "Chromium, Cobalt and Lanthanum in Lung, Liver and Kidney Tissue from Deceased Smelter Workers," Science of the Total Environment 37 (2/3): 233-246 (see particularly 242), August 1, 1984.

32. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.

33. Hartung, R., "Chapter Fifty-Eight. Cyanides and Nitriles. 2. Cyanides. 2.1 Hydrogen Cyanide." In: Patty's Industrial

2025822296

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 4850-4853 (see particularly 4850), 1982.

Honig, D.H., Hockridge, M.E., Gould, R.M. and Rackis J.J., "Determination of Cyanide in Soybeans and Soybean Products," Journal of Agricultural and Food Chemistry 31(2): 272-275, 1983.

Misselhorn, K. and Adam, R., "On The Cyanide Contents in Stone Fruit Products," Branntweinwirtschaft 116(4): 45-50, 1976. English Abstract.

Askar, A. and Morad, M.M., "Lebensmittelvergiftung. 1. Toxine in natürlichen Lebensmitteln (Food Poisoning. 1. Toxins in Natural Foodstuffs)," Alimenta 19: 59-66, 1980. English Summary.

34. Lundquist, P., Rosling, H., Sörbo, B. and Tibbling, L, "Cyanide Concentrations in Blood After Cigarette Smoking, as Determined by a Sensitive Fluorimetric Method," Clinical Chemistry 33(7): 1228-1230, 1987.

35. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 315), October, 1989.

36. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

37. WHO International Agency for Research on Cancer, The Evaluation of the Carcinogenic Risk of Chemicals to Humans, Lyon, World Health Organization, IARC Monograph No. 23, 325-416, 1971.

38. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.

39. Rowe, V.K. and McCollister, S.B., "Chapter Fifty-Six. Alcohols. 2. Methanol." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 4528-4541, 1982.

2025822297

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

Isshiki, K., "Analysis of Methyl and Ethyl Alcohols in Foods and Assessment of Dietary Intake Levels," Shokuhin Eiseigaku Zasshi (Journal of the Food Hygienic Society of Japan) 26(1): 39-45, 1985. English Abstract.

40. Marnett, L.J., "Health Effects of Aldehydes and Alcohols in Mobile Source Emissions." In: Air Pollution, The Automobile and Public Health. Washington, D.C., National Academy Press, 579-603 (at 587), 1988.

41. Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 3. Dinuclear Systems. 3.1 Naphthalene." In: Patty's Industrial Hygiene and Toxicology, Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 3333-3343, 3400-3431, 1982.

42. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312), October, 1989.

43. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer, A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 211), 1982.

44. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

Wynder, E.L. and Hoffmann, D., Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis, New York, Academic Press Inc., 493, 498, 627-628, 1967.

45. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 315), 1989.

46. U.S. Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, "14. Constituents of Tobacco Smoke: Toxicity of Specific Smoke Components," Smoking and Health, A Report of the Surgeon General, DHEW Publication No. (PHS) 79-50066, Washington, D.C., U.S. Government Printing Office, 78-84 (at 80), 1979.

2025822298

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

47. Reinhardt, C.F. and Brittelli, M.R., "Chapter Thirty-Eight. Heterocyclic and Miscellaneous Nitrogen Compounds. 3.2.3. Dimethylnitrosamine." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 2286-2789 (at 2786), 1982.

48. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 311), October, 1989.

49. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 200), 1982.

50. Reinhardt, C.F. and Brittelli, M.R., "Chapter Thirty-Eight. Heterocyclic and Miscellaneous Nitrogen Compounds. 3.2.3. Dimethylnitrosamine." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 2286-2789, 1982.

51. Fishbein, L., "Overview of Some Aspects of Occurrence, Formation and Analysis of Nitrosamines," Science of the Total Environment 13(2): 157-188, 1979.

Pensabene, J., Fiddler, W., Doerr, R.C., Lakritz, L. and Wasserman, A.E., "Formation of Dimethylnitrosamine From Commercial Lecithin and its Components in a Model System," Journal of Agricultural and Food Chemistry 23(5): 979-980, 1975.

Sen, N.P., Smith, D.C., Schwinghamer, L. and Marleau, J.J., "Food Additives: Dimethylnitrosamine and Other N-Nitrosamines in Foods," Journal of the Association of Official Analytical Chemists 52(1): 47-52, 1969.

52. Deichmann, W.B. and Keplinger, M.L., "Chapter Thirty-Six. Phenols and Phenolic Compounds. 1. Phenol." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 2567-2584, 1982.

Babich, H. and Davis, D.L., "Phenol: A Review of Environmental and Health Risks," Regulatory Toxicology and Pharmacology 1(1): 90-109 (see particularly 90, 103), 1981.

2025822299

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

53. Deichmann, W.B. and Keplinger, M.L., "Chapter Thirty-Six. Phenols and Phenolic Compounds. 1. Phenol." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 2567-2584 (at 2583-2584), 1982.

54. Kensler, C.J., Battista, S.P. and Thayer, P.S., "19. Animal Models for the Study of Tobacco Carcinogenesis." In: Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis. Frederick Coulston and Philippe Shubik (eds.). Norwood, New Jersey, Ablex Publishing Corporation, 341-357 (see particularly 351), 1980.

55. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (see particularly 190, 210), 1982.

U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 3. Cancer," The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General, DHHS Publication No. (PHS) 81-50156, Washington, D.C., U.S. Government Printing Office, 75-109 (see particularly 94), 1981.

56. Robertson, G.B. and Rogers, A.W., "An Autoradiographic Search for Radioactive Particles in the Lungs of Cigarette Smokers," Archives of Environmental Health 35(2): 117-122, March/April, 1980.

57. Cohen, B.S., Eisenbud, M. and Harley, N.H., "Measurement of the Alpha-Radioactivity on the Mucosal Surface of the Human Bronchial Tree," Health Physics 39(4): 619-632, 1980.

Harley, N.H., Cohen, B.S. and Tso, T.C., "Polonium-210: A Questionable Risk Factor in Smoking-Related Carcinogenesis." In: Banbury Report 3: A Safe Cigarette? G.B. Gori and F.G. Bock (eds.). Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 93-104, 1980.

58. Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 1.3. Toluene." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 3283-3291, 3400-3431, 1982.

2025822300

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

59. Gibson, J.E. and Hardisty, J.F., "Chronic Toxicity and Oncogenicity Bioassay of Inhaled Toluene In Fischer-344 Rats," Fundamental and Applied Toxicology 3: 315-319, July/August, 1983.

Häsänen, E., Karlsson, V., Leppämaki, E. and Juhala, M., "Short Communication: Benzene, Toluene and Xylene Concentrations in Car Exhausts and in City Air," Atmospheric Environment 15(9): 1755-1757, 1981.

Carpenter, C.P., Geary, D.L. Jr., Myers, R.C., Nachreiner, D.J., Sullivan, L.J. and King, J.M., "Petroleum Hydrocarbon Toxicity Studies. XIII. Animal and Human Response to Vapors of Toluene Concentrate," Toxicology and Applied Pharmacology 36(3): 473-490, 1976.

60. Canas, B.J., Havery, D.C., Robinson, L.R., Sullivan, M.P., Joe, F.L., and Diachenko, G.W., "Ethyl Carbamate Levels in Selected Fermented Foods and Beverages," Journal of the Association of Official Analytical Chemists 72(6): 873-876, 1989.

Ingledew, W.M., Magnus, C.A., and Patterson J.R., "Yeast Foods and Ethyl Carbamate Formation in Wine," American Journal of Enology Viticulture 38(4): 332-335, 1987.

Mossoba, M.M., Chen, J.T., Brumley, W.C., and Page, S.W., "Application of Gas Chromatography/Matrix Isolation/Fourier Transform Infrared Spectrometry to the Determination of Ethyl Carbamate in Alcoholic Beverages and Foods," Analytical Chemistry 60(9): 945-948, May 1, 1988.

61. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (see particularly 194), 1982.

62. Squirrell, D.C. and Thain, W., "Environmental Carcinogens--Selected Methods of Analysis," IARC Publications, Monograph No. 22, 113-120, 1978.

Albanus A.L., Gawell, B.-M., Larsson, B. and Slorach, S.A., "Sänkt maximigräns för vinylklorid i livsmedel (Reduced Maximum Tolerance for Vinyl Chloride in Foods)," Var Föda 31(3): 161-168, March, 1979. English Summary.

2025822301

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000

63. Torkelson, T.R. and V.K. Rowe, "Chapter Forty-Eight. Halogenated Aliphatic Hydrocarbons. 3. Unsaturated Halogenated Hydrocarbons. 3.1. Vinyl Chloride." In: Patty's Industrial Hygiene and Toxicology, Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3537-3542, 3595-3596 (see particularly 3537), 1982.

64. Hoffmann, D., Patrianakos, C. and Brunnemann, K.D., "Chromatographic Determination of Vinyl Chloride in Tobacco Smoke," Analytical Chemistry 48(1): 47-50 (at 50), January, 1976.

65. Huber, G.L, "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 316), October, 1989.

2025822302

Source: https://www.industrydocuments.ucsf.edu/docs/rgkj0000